A RANDOMIZED CLINICAL TRIAL ON
MANAGEMENT OF EARLY PREGNANCY FAILURE (MEPF)

National Institute of Child Health and Human Development
National Institutes of Health

In Collaboration with:

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PROTOCOL

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1. INTRODUCTION

Medical management with misoprostol for early pregnancy failure has been increasingly used in recent years. However, the efficacy and acceptability have yet to be established in a large randomized trial. We plan to conduct a multicenter, randomized clinical trial comparing misoprostol treatment with vacuum aspiration (D&C, the current standard of care) for early pregnancy failure.

1.1 SUMMARY

We propose a two-arm, randomized trial on efficacy, safety and acceptability of misoprostol treatment for early pregnancy failure. The study population will consist of 800 pregnant women who have an incomplete spontaneous abortion, anembryonic gestation, embryonic/fetal demise or inevitable abortion in the first trimester. At enrollment and prior to randomization, medical history will be collected. We will perform a physical examination, characterize the pregnancy by transvaginal ultrasound, and collect a blood sample for confirmatory laboratory tests. Subjects will complete baseline questionnaires regarding demographic characteristics and symptoms.

The subjects will be randomly assigned to receive either misoprostol 800 µg per vagina or D&C. Subjects receiving misoprostol will return on Day 3. If the expulsion of product of conception has not completed, a second dose of 800 µg of vaginal misoprostol will be given. On Day 8, if the expulsion of product of conception still has not completed, D&C will be offered. All subjects will come back for follow-up visit on Day 15.

All subjects will complete daily diaries regarding bleeding, pain and other symptoms until 2 weeks after initial treatment. They will undergo follow-up ultrasound exams and laboratory tests, and will be interviewed regarding treatment complications, adverse events, and use of medications during the follow-up period. They will also be asked to complete a questionnaire regarding anxiety, satisfaction and cost at the final follow-up visit on Day 15. On Day 30, the subjects will be contacted by telephone and asked regarding any symptom and treatment since the last visit. We will compare the success rate, side effects and acceptability between these two groups.

1.2 PRIMARY HYPOTHESIS

Medical treatment with 800 µg vaginal misoprostol is as effective as vacuum aspiration in managing early pregnancy failure.

1.3 PURPOSE OF THE STUDY PROTOCOL

This protocol describes the background, design and organization of the study and may be viewed as a written agreement between the study investigators. It is prepared by the Steering Committee, reviewed by the Data and Safety Monitoring Committee, and is approved by the Institutional Review Board of relevant parties before recruitment begins. Any changes to the protocol during the study require the approval of the Steering Committee and IRB and by the Data and Safety Monitoring Committee.

A Procedure Manual supplements the protocol with detailed specifications of the study procedures.

2. BACKGROUND AND SIGNIFICANCE

2.1 INTRODUCTION

Early pregnancy failure, including spontaneous abortion and nonviable conception, occurs in 15% of clinically recognized pregnancies (Alberman). Approximately one in four women experience early pregnancy failure during her lifetime. For the most part of the last century, dilation and curettage (D&C) has been the commonly accepted management for the early pregnancy failure. The purpose of this procedure is to ensure that the products of conception are completely evacuated from the uterus as soon as possible in order to minimize blood loss and the risk of upper genital tract infection (Jurkovic). This practice may be traced back to late 19th century and early 20th century when illegally induced abortions were common and risks of hemorrhage and sepsis were a serious threat to maternal morbidity and mortality (Hertig, Dunn). Over the years, surgical evacuation of retained products of conception in early pregnancy failure has become universally accepted as the treatment of choice or the standard of care. Although vacuum aspiration or suction curettage has largely replaced sharp curettage, D&C is still one of the most common outpatient procedures in gynecologic patients (Owings). With the availability of antibiotics and legalization of abortion, many of the above problems have been eliminated. In recent years, the medical community began to question whether immediate evacuation by surgical intervention is truly necessary for most cases of early pregnancy failure (Macrow, Ballagh, Jurkovic).

In the past decade, two lines of literature have emerged. Several clinical trials and observational studies have explored the efficacy of expectant and medical management for early pregnancy failure. The following paragraphs briefly review the existing literature on this topic.

2.2 EXPECTANT MANAGEMENT FOR EARLY PREGNANCY FAILURE

Empirical evidence suggests that immediate surgical intervention may not be necessary in patients who do not present with heavy bleeding, anemia, unstable vital signs or evident signs of infection. Expectant management or watchful waiting becomes a natural alternative. To examine the efficacy of this management, three randomized clinical trials and two observational studies have been conducted so far.

Nielsen and Hahlin (1995) randomized 155 women with incomplete spontaneous abortion to expectant management (N=103) or D&C (N=52). All women had a uterine lining measured by transvaginal ultrasound examination between 15 and 50 mm in diameter. Effective treatment was defined as a reduction of uterine contents to less than 15 mm. In the expectant management group, 79% had spontaneous resolution without intervention in 3 days. Compared with the D&C group, rates of infection or anemia in the expectant group were slightly lower; bleeding was slightly prolonged; but the hemoglobin levels and days of pain were similar. In a smaller trial, Chipchase and

James (1997) randomized 35 women with "retained products" (intrauterine tissue of <50 mm in diameter per transvaginal ultrasound exam) to either expectant group (N=19) or D&C (N=16). All women in the expectant group had spontaneous completion. Intrauterine infection occurred in one woman in each group. Women in the expectant group bled for an average of 4 days compared to 2 days in the surgical group. The days of pain and sick leave were similar. The expectant management was well accepted.

Nielsen et al. (1999) randomized 122 women with inevitable or incomplete abortions < 13 weeks who had retained products of conception with an anterior-posterior diameter between 15 and 50 mm to treatment with mifepristone 400 mg orally followed by a single oral dose of 400 µg misoprostol 48 hours later (n=60) or expectant management (n=62). 76% of those randomized to expectant management had an empty uterine cavity after five days versus 82% for the medical management group (p=0.6).

However, two observational studies showed less success with the expectant management. Jurkovic et al. (1998b) prospectively followed 85 women with missed abortion who chose to have expectant management. Only 25% had a complete spontaneous resolution. Fourteen women were diagnosed with incomplete abortion requiring D&C and 50 elected D&C because of no expulsion. Of those women who elected surgery, more than half elected surgery within 7 days and 70% did so within the first 14 days. Thus, the high failure may have been due, in part, to poor counseling, inappropriate expectations on the part of the patients, or both. It should also be pointed out that the subgroup of women with smaller gestational sacs and earlier gestational ages was more likely to complete successfully without intervention.

In a retrospective chart review, Hurd et al.(1997) examined 63 women with first trimester fetal demise who also had significant intrauterine tissue, defined as an intrauterine gestational sac >10 mm in mean diameter by vaginal ultrasound. The mean gestational age was 8.5 weeks. Twenty-four women were managed expectantly. Spontaneous, complete expulsion occurred in 15 of 24 patients (63%). Among the nine patients who received D&C, 5 were incomplete, 3 missed, and 1 septic abortion. One of them required blood transfusion. The authors also reported that among 81 women with intrauterine tissue less than 10 mm and managed expectantly, all of them aborted spontaneously.

These data, though very limited, seem to suggest that incomplete or inevitable abortion with small amount of tissue may be suitable for expectant management with a high success rate. In a multivariable analysis, Nielsen (1995) identified serum progesterone level, hCG change and intrauterine diameter as independent predictors for success. The success rate appears lower in missed abortions with much longer waiting period. This may limit its use due to patient's anxiety and emotional distress after miscarriage. Therefore, a medical management for early pregnancy failure may offer an alternative to both surgical and expectant management.

2.3 PHARMACOLOGY OF MISOPROSTOL

The purpose of medical management is to induce uterine contraction to expel retained products of conception after embryonic or fetal demise. Prostaglandins and analogues have been used in previous studies with various regimens. One of the drugs is misoprostol (Cytotec, Searle). Misoprostol (methyl 11, 16 dihydroxy-16-methl-9-oxyoprost-13E-en-oate) is a prostaglandin E_1 analogue that has been approved by the Food and Drug Administration (FDA) to be taken orally for the prevention and treatment of gastric ulcers associated with the use of nonsteroidal antiinflammatory drugs. It has also become an important drug in obstetrical and gynecologic practice because of its uterotonic and cervical-ripening actions. Misoprostol has been used in elective medical abortion, cervical ripening, evacuation of the uterus in missed abortions, and induction of labor (Goldberg). Furthermore, misoprostol is inexpensive and stable at the room temperature. Before we review the current literature on efficacy and safety of medical management of early pregnancy failure, we briefly describe the pharmacology of misoprostol, which will be used in the current study.

Misoprostol is manufactured as an oral preparation in 100 µg unscored and 200 µg scored tablets. After oral administration, misoprostol is rapidly absorbed and converted to its pharmacologically active metabolite, misoprostol acid. Plasma concentrations of misoprostol acid peak in approximately 30 minutes and decline rapidly thereafter (Figure 1). (Zieman) Misoprostol is primarily metabolized in the liver, and less than 1 percent of its active metabolite is excreted in urine (Foote). Patients with hepatic disease should receive a decreased dose, whereas dose adjustment is unnecessary for patients with renal insufficiency who do not require dialysis (Foote). Misoprostol has no known drug interactions and does not induce the hepatic cytochrome P-450 enzyme system.

The most common adverse effects of misoprostol are nausea, vomiting, diarrhea, abdominal pain, chills, shivering, and fever, all of which are dose-dependent. Although other prostaglandins (prostaglandin E_2 and prostaglandin F_2(a)) can cause myocardial infarction and bronchospasm, misoprostol does not (Ulmann). Toxic doses of misoprostol have not been determined. However, a cumulative dose of up to 2200 µg administered over a period of 12 hours has been tolerated by pregnant women, with no serious adverse effects (el-Refaey). A dose of 6000 µg of misoprostol, taken orally to induce an abortion (in conjunction with trifluoperazine), resulted in abortion, hyperthermia, rhabdomyolysis, hypoxemia, and a complex acid-base disorder (Bond).

The oral preparation of misoprostol administered vaginally enhances the effects of misoprostol on the reproductive tract, and reduces gastrointestinal adverse effects (Danielsson, Creinin 1993, Toppozada). It also avoids the deficiency that the bioavailability of misoprostol is decreased by concomitant ingestion of food or antacids. When misoprostol tablets are placed in the posterior fornix of the vagina, plasma concentrations of misoprostol acid peak in one to two hours and then decline slowly

(Figure 1). Vaginal application of misoprostol results in slower increases and lower peak plasma concentrations of misoprostol acid than does oral administration, but overall exposure to the drug is increased (indicated by the increased area under the curve in Figure 1).

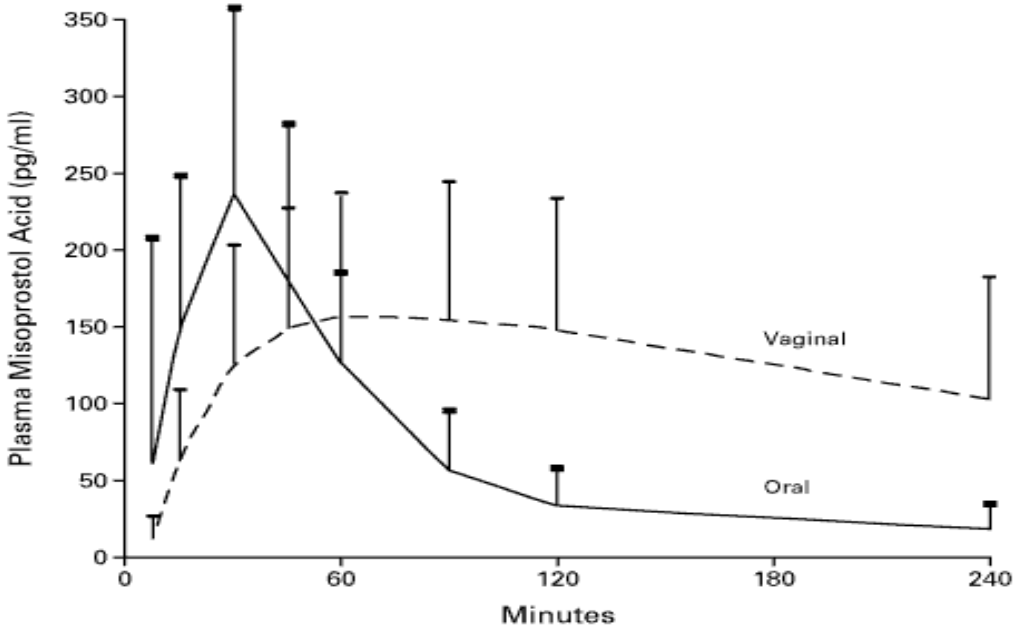


Figure 1. Mean plasma concentrations of misoprostol acid over time with oral (solid line) and vaginal (dotted line) administration. (Zieman, 1997).

Among women who were 9 to 11 weeks pregnant and given misoprostol before a surgical abortion, intrauterine pressure began to increase an average of 8 minutes after oral administration and 21 minutes after vaginal administration and was maximal 25 minutes after oral administration and 46 minutes after vaginal administration. Uterine contractility initially increased and then plateaued one hour after oral administration, whereas uterine contractility increased continuously for four hours after vaginal administration. Maximal uterine contractility was significantly higher after vaginal administration (Danielsson).

2.4 EFFICACY OF MEDICAL MANAGEMENT ON INCOMPLETE OR INEVITABLE SPONTANEOUS ABORTION

Several studies have been published on efficacy of medical management on early pregnancy failure. Given the intuitive assumption that efficacy for incomplete or inevitable abortion may differ from that for anembryonic or missed abortion, two lines of studies are reviewed separately in the following paragraphs. Just like studies addressing treatment issue for many other diseases, studies addressing medical

management of early pregnancy failure are also hampered by the lack of consistency in patient selection, choice and dosage of medication, routes of drug application, and follow-up criteria documenting complete miscarriage.

There have been eight studies on medical management of incomplete or inevitable miscarriage using prostaglandin analogues such as misoprostol (Henshaw, deJonge, Chung 1994, 1995, 1997, 1999). Henshaw et al.(1993) enrolled 44 women with sonographically and clinically proven inevitable or incomplete spontaneous abortion at less than 13 weeks of gestation. They were given either a single dose of sulprostone (a synthetic prostaglandin E_2 analog) 0.5 mg intramuscularly or misoprostol 400 µg orally. Since there were no significant differences between these two drugs, the authors combined the results. Women were reviewed 12-18 hours after treatment. Surgical evacuation was performed if there had been no decrease in pain, bleeding or uterine size. Patients were followed up 10-14 days later for clinical and transvaginal ultrasonography. A total of 38 patients completed the study; two received surgical evacuation. The success rate was 95% (95% confidence interval: 89% – 100%).

DeJonge et al. (1995) conducted a randomized clinical trial of 50 patients with a history of amenorrhea followed by abdominal cramping and vaginal bleeding, uterine size up to 14 weeks of gestation, evaluated clinically, dilated cervical os and palpable products of conception. Medical management consisted of a single dose of misoprostol 400 µg orally. And surgical management was curettage. Success was defined as bleeding had reverted to a blood stained discharge, pain had subsided, the uterus was smaller, and the cervical opening had closed on repeat pelvic examination 12 hours after misoprostol administration. Pelvic ultrasonography was performed when uncertainty existed about the completeness of the abortion. Only 3 (13%) of women receiving medical management had a successful evacuation compared with 25 (97%) of the women in the surgical group ($p < 0.001$). The authors suggested that further randomized trials with higher doses and/or vaginal administration, potentially in combination with mifepristone may be indicated to achieve increased efficacy.

Chung and associates conducted a series of studies on medical management of spontaneous abortion (Chung 1994, 95, 97, 99). In the first study, they recruited 132 women with spontaneous abortion at 6-18 weeks of gestation (the mean gestational age of 9 weeks) and transvaginal ultrasound confirmed that there was “significant” amount of tissue left or an intrauterine sac (Chung 1994). Up to 5 gemeprost 1 mg vaginal peccaries were inserted at 3-hourly intervals until a tissue mass consistent with product of conception was passed or complications developed. 60 women required no further treatment while 72 had “significant” amount of tissue or had a choriodecidual reaction but with intrauterine dimensions that were unacceptable for conservative management. The latter women had D&C. Thus, the success rate was 45% (95% CI: 37% – 53%).

In the second study (Chung 1995), the authors followed the same protocol and recruited 141 patients as described above. The patients were given 400 µg of

misoprostol orally every 4 hours for a total of three doses. They were observed in hospital and reassessed on the following morning both clinically and by transvaginal ultrasound. Those who had heterogeneous echogenic material in the cavity of the uterus or who had a well-defined cavity but with unacceptably large dimensions underwent D&C. 88 women did not require D&C (62%, 95% CI: 54 -- 70%).

In the third study (Chung 1997), the authors recruited 225 similar patients with spontaneous abortion. Up to a total of 1200 µg of misoprostol were given orally in 3 divided doses each day for up to 2 days. A choriodecidual reaction measuring less than 5 cm^2 in the transverse and sagittal planes was considered empty provided there were no identifiable product of conception within the uterine cavity. Among these 225 women who received a 1200 µg misoprostol in 3 divided doses, 107 women had emptied the uterus within 24 hours. Eleven women were excluded from the second course (7 refused to continue; 2 had heavy blooding; 2 had temperature over 38°C) and had D&C. The remaining 107 women were given a second course of 1200 µg misoprostol. Forty-two emptied the uterus within 24 hours and the remaining 66 patients received D&C. The cumulative success rate was 66% (95%CI: 60 – 72%).

More recently, Chung and associates (1999) conducted a large randomized trial comparing surgical evacuation with medical management with misoprostol for spontaneous abortion. A total of 635 women with a mean gestational age of 11 weeks were randomly assigned to either D&C or misoprostol. 308 women were given 400 µg of misprostol orally every 4 hours up to a total dose of 1200 µg. All cases were observed in the ward, and a transvaginal ultrasound was performed the next day. Those who still had significant tissue received D&C. 159 women received D&C, yielding the success rate of 48% (95% CI: 42 – 54%). In comparison, women who were assigned to the D&C group, 96% (95%CI: 94 – 98%) received D&C once, which is considered as a success.

Pandian et al. (2001) reported their experience with 600 µg of oral misoprostol followed by two further oral doses of 400 µg at two-hourly intervals. Ninety-five of 112 women (85%) with incomplete miscarriage between 6 and 13 weeks' gestation completed uterine evacuation without the need for surgical evacuation.

Nielsen et al.(1999) randomized 60 women with inevitable or incomplete abortion to mifepristone 400 mg followed 36 hours later by misoprostol 400 µg orally and 62 women to expectant management. Only women with an endometrial lining between 15 and 50 mm by transvaginal ultrasound were included. Two days after misoprostol treatment for the medical management group, the expulsion rates were 82% and 76% in the medical and expectant management groups (p=0.62).

A number of factors need to be considered in these studies which had very different results. First, there are significant differences in patient selection. In the study with the best results, all patients with the diagnosis of missed abortion were excluded. Other studies included both incomplete miscarriages and those with an intact sac, and

with more advanced gestation, which may have contributed to the lower success rate. Furthermore, in the study with the lowest success rate (DeJonge), ultrasound was not used before administering treatment. Therefore, it is possible that cases of threatened miscarriages were treated and included in the analysis (Jurkovic (I)).

2.5 EFFICACY OF MEDICAL MANAGEMENT FOR ANEMBRYONIC GESTATION AND MISSED ABORTION

Two recent prospectively randomized trials address the role of medical management on anembryonic gestation and missed abortion. Creinin et al (1997) randomized 20 women with ultrasononographically diagnosed non-viable early pregnancy failure up to 8 weeks of gestation, with a closed cervical os and minimal vaginal bleeding to either misoprostol 400 µg orally or 800 µg vaginally. Subjects returned 24 hours after treatment for a transvaginal ultrasound examination. If the gestational sac was still present, the second dose of misoprostol was given and the patient returned after 24 hours. Subjects who failed to expel the product of conception were offered D&C. In patients who received oral misoprostol, complete uterine evacuation occurred in three of twelve (25%) and in the vaginal misoprostol group, complete uterine evacuation was seen in seven of eight women (88%) (p=0.01). This study demonstrated that vaginal misoprostol 800 µg is more effective than oral misoprostol 400 µg for uterine evacuation of early pregnancy failure.

In another small study, Autry et al.(1999) recruited 21 women with non-viable pregnancy up to 49 days gestation. 12 women were randomized to receive intramuscular methotrexate, followed 2 days later by vaginal misoprostol 800 µg. Nine women were randomized to receive vaginal misoprostol 800 µg alone. All patients returned next day for ultrasound. If the gestational sac was present, vaginal misoprostol was repeated and the patient was instructed to return in 10-14 days for a follow-up examination and ultrasound. All 12 women in the combined group (100%) and eight of nine in the misoprostol only group (89%) had successful complete abortion. The single failure presented within 12 hours after the first dose of misoprostol with heavy vaginal bleeding and underwent a D&C. Three patients in the combined group and five patients in the misoprostol only group received two doses of misoprostol.

Four studies used a combination of mifepristone and prostagladins to treat missed abortions. El-Refaey et al. (1992) recruited 59 patients with a diagnosis of missed abortion or anembryonic pregnancy equivalent to 13 weeks' gestation or less. They were given mifepristone 600 mg followed 48 hours later by misoprostol 600 µg orally in a divided dose (400 µg and, two hours later, 200 µg). Eight patients aborted with mifepristone alone. Of the 51 remaining patients, 43 aborted after taking misoprostol 600 µg and five more aborted after receiving a second divided dose of 600 µg misoprostol. In three patients the treatment failed and received D&C. Therefore, the success rate was 95% (95%CI: 92 – 98%). In a second, partially randomized trial by the same group (Kim,1997), women with missed abortion were given 200 mg mifepristone followed by three sequential oral doses of 400/600/400 µg misoprostol 2 h

apart. A total of 129 women received medical treatment and 224 surgical. The efficacy for those with gestation <71 days or sac diameter <24 mm was 92% and 94%, respectively. These success rates were equivalent to surgical evacuation (98%, p=0.5). The efficacy for pregnancies with gestation 71 – 144 days or sac diameter 24 – 77 mm was 86% and 84%, respectively.

However, other authors did not achieve similar success. Nielsen et al.(1997) prospectively evaluated 31 women with missed abortion (endometrial lining of 15 – 50 mm in diameter by transvaginal ultrasound) who were treated with mifepristone 400 mg followed 36 hours later by misoprostol 400 µg orally. Only 16 (52%) women completely aborted within 6 days.

To determine whether moistening the misoprostol tablets increases the efficacy of the regimen, a recent randomized study compared moistened with dry tablets of misoprostol (800 µg) in combination with methotrexate for induced abortion in 240 women who were no more than 49 days pregnant. (Creinin, 1999). There was no significant difference in the rate of complete abortion (95 percent with moistened tablets and 92 percent with dry tablets, P=0.40.) In a randomized study comparing moistened and dry tablets of misoprostol alone (800 µg) in 80 women who were no more than 63 days pregnant, there was also no significant difference in the rate of complete abortion (85 percent with moistened tablets and 65 percent with dry tablets, P=0.43) (Ngai).

Based on these small studies, it appears that the combination of mifepristone 400 mg followed by oral misoprostol 400 µg does not provide significant advantages over vaginal misoprostol 800 µg alone for the treatment of missed abortion or anembryonic gestation. However, since the success rate may be confounded by gestational age, the efficacy of either regimen has yet to be established.

2.6 SAFETY OF MEDICAL MANAGEMENT FOR EARLY PREGNANCY FAILURE

Numerous studies, mostly from literature on medical abortion, have demonstrated that misoprostol is very safe. FDA has recently approved its use in conjunction with mifepristone for medical abortion. The common side effects related to vaginal or oral misoprostol use include cramping, nausea, vomiting and diarrhea. Less common but more severe complications are heavy bleeding, fever and infection (pelvic inflammatory infection), which often demand immediate surgical intervention, i.e., D&C. Table 1 summarizes the incidence of the side effects in the previous studies of medical management of early pregnancy failure. These studies suggest that the rate of serious complications with misoprostol is similar to that with D&C. For instance, the post-procedural infection rate in women having a suction curettage for incomplete abortion was 6.3% in a recent report (Prieto, 1995). And the rate of infection was not different in patients who received prophylactic antibiotics. Another serious complication related to D&C is uterine perforation. It ranges from 0.2% to 1.5% in the United States (Grimes, 1979). This complication can be almost totally avoided with misoprostol. Therefore,

medical management of early pregnancy failure appears as safe as D&C. Severe complications were rare.

This conclusion is further highlighted in a recent randomized clinical trial on vaginal misoprostol 800 µg administered 1, 2, or 3 days after mifepristone for early medical abortion (Schaff, 2000). This was by far the largest trial which included 2295 healthy patients with less than 57 days of pregnancy. Patients received 200 mg of oral mifepristone and were randomly assigned to self-administer 800 µg of vaginal misoprostol at home 1, 2, or 3 days later. The results showed that there was no difference in efficacy or side effects when misoprostol was administered 1, 2, or 3 days after mifepristone. Although this trial is not directly related to the management of early pregnancy failure, it provides valuable information regarding safety and acceptability of use of 800 µg vaginal misoprostol. 86% of patients started to bleed within 4 hours of using misoprostol. An additional 12% started bleeding between 4 and 24 hours after inserting misoprostol. Only 13 (0.6%) unexpected or serious adverse events occurred: 2 pelvic infection (treated with i.v. antibiotics), 2 endometritis (treated with oral antibiotics), 2 transient rashes, 1 vasovagal reaction to cramping pain (treated with i.v. fluids), 2 excessive bleeding (treated with i.v. fluids), 2 vomiting and dehydration (treated with i.v. fluids), 1 panic attack, and 1 extreme irritability similar to premenstrual syndrome. In the follow-up acceptability survey, 88% women considered that bleeding was acceptable; 74% women thought that pain was acceptable; and 84% patients rated the overall adverse effects acceptable. In addition, 90% subjects responded that home self-administer of misoprostol was acceptable.

According to FDA, there was one case reported to FDA in which a woman who had a ruptured uterus requiring a hysterectomy after one dose of misoprostol 800 ug given vaginally. She was 8 weeks pregnant by ultrasound and had 1 previous Cesarean section. FDA acknowledged that since the total number of women exposed to this dose of vaginal misoprostol in the first trimester is not known, the risk of ruptured uterus is not known.

2.7 RATIONALE AND SIGNIFICANCE

It becomes clear that vaginal misoprostol can potentially be a safe, effective alternative to D&C in managing early pregnancy failure. It has several advantages over D&C. First, women will have a choice over a surgical management. Second, it will reduce the physician and hospital burden, especially where D&C is performed in an operating room. This has been a prominent problem in hospitals that provide health care to a large number of patients (Leveno, personal communication). It will probably be less expensive. Third, family practitioners may be able to take care of more patients with early pregnancy failure (Wiebe, 1998). Indeed, misoprostol is well received by family practitioners as an alternative management. Furthermore, in developing countries, especially in rural areas where health care resources are extremely limited, post-D&C infection is common, which causes significant maternal morbidity and

mortality. If D&C can be avoided in most cases of early pregnancy failure by using misoprostol, it is likely to reduce maternal morbidity and mortality in underdeveloped nations. However, the efficacy, safety and acceptability of misoprostol management have yet to be established in a large, controlled clinical trial before its widespread use. This is the main purpose of our study. Results from this trial will provide clinicians in the U.S. with crucial information for patient care and guidance for potential application in developing countries.

Table 1
Adverse Effects of Misoprostol for Medical Management of Early Pregnancy Failure

Author (year)	Total N	Regimen	Cramps	Vomiting	Diarrhea	Heavy Bleeding	Fever	Infection	Oral Analgesia	i.m. analgesia	Other
Henshaw (1993)	44 incomplete < 13 wks	Oral 400 ug or 0.5mg sulprostone				1			11	2	
DeJonge (1995)	50 incomplete ? 14 wks	Oral 400 ug	"No drug Related Complications Were Encountered								
Chung (1994)	132 incomplete 6 – 18 wks	Vaginal 1mgX5 gemeprost	32 (24%)	24 (17%)	15 (11%)						
Chung (1995)	141 incomplete 6 – 18 wks	Oral 400 ug/4hx 3		2	5		13 (T>37.5C)	3 (4%vs.3% for D&C)			3 head ache,1 dizzy
Chung (1997)	225 incomplete 6 – 18 wks	Oral 400 ug/4hx 3				2	2 (T>38C)	2	34	27	
Chung (1999)	309 incomplete 6 –18 wks	Oral 400 ug/4hx3	4			3		9	70	19	
Creinin (1997)	12 missed ? 8 wks	Oral 400 ug		3	5				11	1	
	8 missed ? 8 wks	Vaginal 800 ug		1	3				8		
Autry (1999)	21 missed ? 7 wks	Vaginal 800 ug				1		0	8		
Kim (1997)	75 incomplete	Oral 2 h apart 400/200 ug								0	
Kim (1997)	129 missed <144 days	Oral 2 h apart 400/600/400ug				3		7 vs. 13% for D&C		19	
El-Refaey (1992)	60 missed ? 13 wks	Oral 600 ug		5	7				13	7	
Nielsen (1997)	31 missed 15–50 mm	Oral 400 ug	2			2					
Nielsen (1999)	60 incomplete 15–50 mm	Oral 400 ug	Pain and bleeding were similar to expectant management								
Pandian (2001)	112 incomplete 6– 13 wks	Oral 600/400/400ug 2 h apart				1		3			

3. STUDY DESIGN

3.1 PRIMARY RESEARCH QUESTIONS

This study will address the primary research question: Is medical management with misoprostol for early pregnancy failure as effective as surgical management with vacuum aspiration?

3.2 SECONDARY RESEARCH QUESTIONS

- Is misoprostol treatment a safe management for early pregnancy failure?
- Is misoprostol treatment as well received as D&C by the patients?
- Is misoprostol treatment as cost-effective as D&C?
- What are the predictors/indicators for a successful misoprostol treatment?

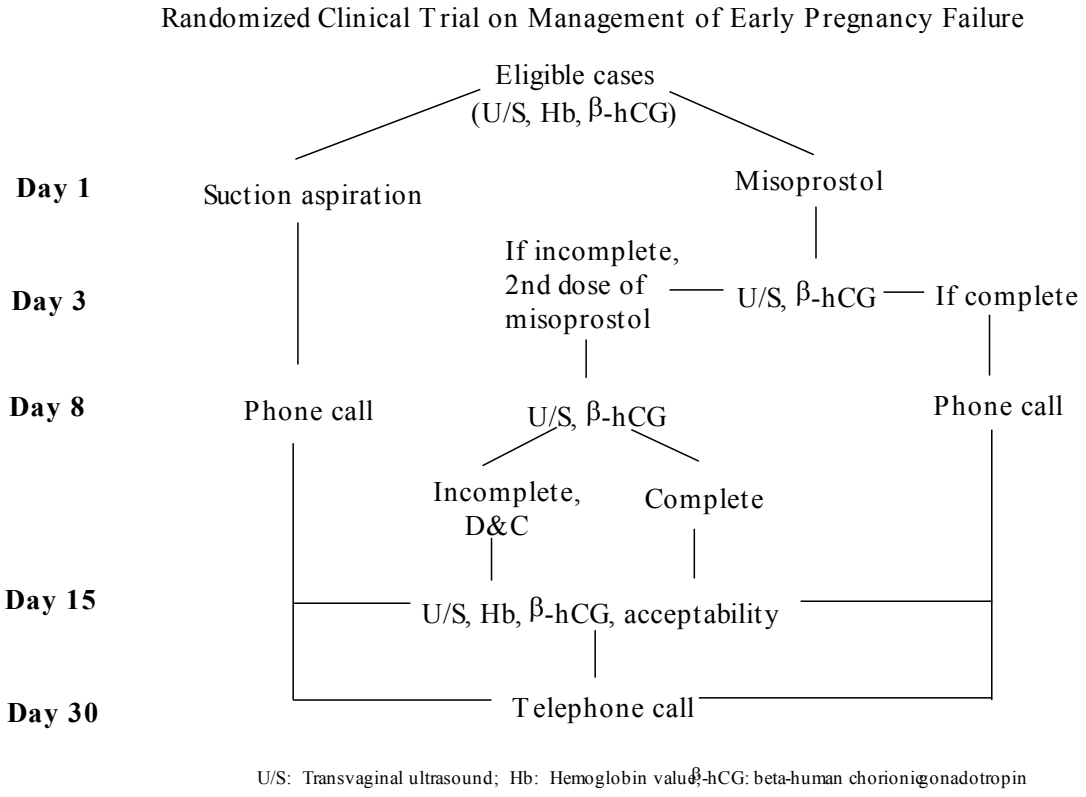
3.3 DESIGN SUMMARY

We propose a two-arm, randomized trial of management for early pregnancy failure. The study population will consist of 800 pregnant women with an incomplete or inevitable spontaneous abortion, anembryonic gestation or fetal demise in the first trimester. At enrollment and prior to randomization, we will collect a detailed medical history, perform a physical examination, characterize the pregnancy using transvaginal ultrasound, and blood for confirmatory laboratory tests. Subjects will complete baseline questionnaires regarding demographic characteristics and symptoms.

Randomization will be performed after consent. Allocation will be 25% to conventional surgical treatment and 75% to medical management. Subjects assigned to surgical treatment will undergo D&C within 24 hours after enrollment. Subjects assigned to medical management will receive 800 μg of vaginal misoprostol on the same day as enrollment (Figure 2). Subjects receiving misoprostol will return on Day 3. If the expulsion of product of conception has not completed, a second dose of 800 μg of vaginal misoprostol will be given. On Day 8, if the expulsion of product of conception still has not completed, D&C will be offered. All subjects will come back for follow-up visit on Day 15.

All subjects will complete daily diaries regarding bleeding, pain and other symptoms until 2 weeks after initial treatment. They will undergo follow-up laboratory tests after initial treatment, and will be interviewed regarding treatment complications, adverse events, and use of medications during the follow-up period. They will also be asked to complete a questionnaire regarding anxiety, satisfaction and cost at the final follow-up visit on Day 15. On Day 30, the subjects will be contacted by telephone and

asked regarding any symptom and treatment since the last visit. We will compare the success rate, side effects and acceptability between these two groups.



U/S: Transvaginal ultrasound; Hb: Hemoglobin value; β-hCG: beta-human chorionic gonadotropin

3.4 ELIGIBILITY CRITERIA

3.4.1 Diagnosis of Early Pregnancy Failure

An early pregnancy failure is defined as a non-viable pregnancy or an incomplete or inevitable abortion in the first trimester (12 weeks or less). The diagnosis will be confirmed with transvaginal ultrasound examination classified as follows:

Non-viable pregnancy: closed internal os, no passage of products of conception, and one of the following ultrasound findings:

- embryonic pole or crown-rump length (CRL) greater than 5 mm without cardiac activity (fetal/embryonic demise) (Goldstein 1992);
- a gestational sac of greater than 16 mm in mean diameter and without an embryo (anembryonic gestation) (Rowling 1997);
- a gestational sac grows < 2 mm over 5 days or < 3 mm over 7 days (Nyberg);

- abnormal rise in serum β-hCG level (<15% increase over 2 days) with a yolk sac present (Creinin 1997).

Diagnosis of embryonic demise may sometimes be difficult, particularly in very early gestation (CRL<10 mm, equivalent to gestational age of 7 weeks). Therefore, a careful work-up according to the standard clinical practice is paramount before the diagnosis of embryonic demise is made. Every effort must be made to ensure that no cardiac activity be detected in the transvaginal ultrasound examination. In compliance with the Federal Regulations, the initial diagnosis of nonviable pregnancy must be made by a physician other than the study investigators. The patient is then referred to the study investigators. The investigators have the responsibility to review the findings with the physician or repeat the ultrasound, if necessary. If there is any uncertainty, a confirmatory ultrasound exam must be taken by the investigators several days later to ensure that absolutely no cardiac activity be identified. Only then will the patient be a potential candidate for recruitment.

Incomplete spontaneous abortion: assumed passage of some products of conception with endometrial tissue (anterior-posterior diameter) ≥ 30 mm (Harwood, as well as our pilot study) and uterine size < 13 weeks.

- **Inevitable abortion:** an intrauterine gestational sac on ultrasound and an open internal cervical os to digital examination with active vaginal bleeding.

3.4.2 Inclusion Criteria

Healthy pregnant women who are diagnosed as having an early pregnancy failure (see diagnostic criteria above) and meet the following criteria by transvaginal ultrasound measures, will be considered as a potential candidate for the study:

- **Non-viable pregnancy**: the embryonic pole or CRL between 5 mm and 40 mm or a gestational sac between 16 mm and 45 mm of mean diameter if CRL unavailable.
- **Incomplete spontaneous abortion**: anterior-posterior endometrial lining greater than 30 mm and uterine size less than 13 weeks;
- **Inevitable abortion**: an intrauterine gestational sac with or without yolk sac or embryonic pole on ultrasound with the following findings:

    - an open os by digital exam;
    - active bleeding;
    - uterine size < 13 weeks;
    - sac size < 46 mm;
    - crown-rump length < 41 mm.

In addition, each subject must meet all the following criteria:

- willing to accept randomization;
- willing to comply with the study protocol and follow-up visit schedule;
- access to telephone and able to provide detailed contact information;
- willing and able to sign the informed consent;
- adequate venous access for phlebotomy.

If a patient has an IUD in situ, she may be eligible after the IUD is removed. It should also be mentioned that our study does not have age limit for participation because both misoprostol and D&C treatments are suitable for pregnant women at all age. A minor, defined by individual State law, will be required to have a parental consent and minor's assent for participation in this study.

3.4.3 Exclusion Criteria:

- orthostatic hypotension, defined as a postural decrease of 20 mmHg in systolic or 10 mmHg in diastolic blood pressure;
- have ovarian hyperstimulation syndrome at the current pregnancy (defined as clinical and ultrasound findings following the ovarian stimulation with gonadotropin or clomiphene citrate resulting in any of the following symptoms: 1) abdominal distention/discomfort, nausea, vomiting and diarrhea; 2) ultrasound evidence of cystic ovarian enlargement greater than 5 cm; or 3) ultrasound evidence of ascites) (Whelan III).
- contraindication to misoprostol (glaucoma, mitral stenosis, poorly controlled seizure disorder, known allergy to prostaglandin);
- have undergone surgical or medical abortion provided by other physicians or self-induced for the current pregnancy prior to enrollment;
- known or suspected ectopic pregnancy;
- known or suspected pelvic infection (temperature $>$38 °C, purulent vaginal discharge, or significant cervical motion tenderness);
- initial hemoglobin < 9.5 mg/dL;
- known clotting disorder (thrombocytopenia: platelet <150,000 per µl or von Willebrand's disease, prolonged prothrombin time (PT) and partial thromboplastin time (PTT)) or use of anticoagulants;
- cardiovascular disease (angina, valvular disease, arrhythmia, or cardiac failure, uncontrolled hypertension);
- currently breast-feeding;
- mental conditions (e.g., depression) or circumstances (e.g., spouse abuse) that are deemed unsuitable for participating in the study;
- concurrent participation in any other interventional trial;
- karyotyping of the fetal tissue is required;
- suspected or confirmed endometrial arteriovenous malformation;
- had been enrolled in this study before.

3.5 STUDY OUTCOME MEASURES AND ASCERTAINMENT

Success: Defined as completion of the process using the intended treatment approach. In the misoprostol group, subjects must complete uterine evacuation without surgical evacuation within 30 days after the initial treatment.

Failure: Defined as a surgical evacuation *at anytime* within 30 days and *for any reason* after initial treatment.

Safety: Defined by the incidence of serious adverse events in each group. These adverse events will include hemorrhage resulting in blood transfusion, uterine perforation resulting in unintended/additional surgery, hospitalization, and death. Previous studies showed that the risk of blood transfusion in patients with D&C was 0.06% and uterine perforation 0.2% (Grimes). With misoprostol, the incidence of heavy bleeding with or without blood transfusion was 0.9% (Chung 1997, 1999). Heavy bleeding occurred in 0.6% of patients managed expectantly.

Side effects: Defined as severe symptoms that may or may not lead to medical or surgical intervention. They include vomiting, diarrhea, fever (38°C), pelvic infection, and emergency room visits. Nausea, vomiting, diarrhea or fever occurs to one-third of patients who use vaginal misoprostol after mifepristone (Schaff). These side effects are usually mild and transient. Pelvic infection occurs in 0.75% of women with D&C (Grimes). According to the literature on medical abortion using misoprostol, the incidence of pelvic infection was less than 0.5% in several large trials (Kruse).

Acceptability: Defined by responses to questionnaires completed by study subjects after the completion of treatment. These will include direct questions regarding preference, severity of side effects, overall acceptance, as well as survey instruments to assess quality of life, anxiety, and other issues during the treatment process.

Cost analysis: Direct and indirect costs and expenses related to medical and surgical treatments and loss of productivity will be collected from the subjects and from the clinical sites for charges of procedures and treatment.

3.6 INFORMED CONSENT CRITERIA

Written informed consent must be obtained before entry into the trial. Full disclosure of the nature and potential risks of participating in the trial is to be made. A parental consent and minor's assent form will also be developed for a minor who is required by the law of individual State to obtain parental consent. Each clinical center will develop its own consent forms, which should be consistent with the model consent

forms and in accordance with the requirements of its Institutional Review Board. Investigators at each institution will work with their IRB to develop an effective sampling and monitoring strategy to insure that the approved procedures are being followed.

3.7 RANDOMIZATION METHOD

Randomization will be stratified by the four clinical sites and type of pregnancy failure (incomplete and inevitable spontaneous abortion versus non-viable pregnancy) to ensure balance between the two groups with respect to anticipated differences in the clinic population and possible differences in patient management. Randomly permutated blocks will be used. Within each block, patients will be randomized in a 3:1 ratio of misoprostol to D&C, i.e., for every one subject assigned to the D&C treatment, three subjects will be assigned to misoprostol treatment. This ratio was chosen mainly because efficacy and safety of D&C are well established while literature on medical management of early pregnancy failure is still limited. Over sampling of subjects for misoprostol without compromising statistical power will provide more valuable information on medical management of early pregnancy failure (See additional justification in Section 5.1). To achieve a more balanced comparison and increase efficiency of the study, we choose to use 3:1 randomization.

An Automated Telephone Response System (ATRS) will be established for clinical site staff to use to request treatment allocations as eligible patients are identified. The ATRS system is accessible only to study personnel who enter the password for the clinical site and his/her assigned personal identification number. Access to the ATRS is obtained by calling a toll free telephone number. The ATRS prompts authorized users by asking prerecorded questions; users respond by pressing keys on a touch-tone telephone. The prerecorded questions include confirmation that the patient meets all inclusion criteria and has no exclusion criteria and whether the woman has given informed consent for enrollment. Depending on the answers to these items, the next available treatment allocation is issued. The treatment allocation is given over the telephone by a prerecorded voice message and confirmed by fax transmission to the clinical site. The date and time of the completion of the call is the time of study entry for each patient. A computer record is maintained for each attempt to enroll a patient using the ATRS.

3.8 RECRUITMENT OF MINORITIES

The four clinical centers are all located in the inner cities with a large representation of minority groups. Specifically, University of Miami, Miami, and Columbia University, New York, have a large percentage of Hispanic population, while University of Pennsylvania, Philadelphia, has a high proportion of African American population. University of Pittsburgh, Pittsburgh, has a predominantly white population. Overall, according to the patient population from these centers, we expect that our study population will be composed of 35% non-Hispanic white, 30% non-Hispanic

black, 30% Hispanic, and 5% others, including Asians and multi-racial. Effort will be made to recruit women with adequate representation of minority groups.

4. STUDY PROCEDURES

4.1 RECRUITMENT

4.1.1 Screening for Eligibility

Patients may come from several sources: hospital emergency room, private physicians or other clinics, and private or clinic patients seen by the investigators. Women who experience vaginal bleeding may go to emergency room. An early pregnancy failure will first be diagnosed by an ER physician. The patient will be informed of the current study. If she expresses her interest in the study, she will be referred to the investigators. Similarly, if a potential candidate is identified by private physicians or in other clinics (such as family planning clinic), she may be referred to the study. However, if a patient is seen by the investigator, he/she must ask another physician who is not involved in this study to make a diagnosis.

When a potentially eligible patient is identified or referred, a project staff will approach the patient and explain to her the purpose of the study, procedures involved, risks, benefits, and alternative treatment. She will answer any questions that the patient may have. If the patient is willing to participate in the study, the project staff will ask her to sign a consent form. All clinical centers have designated research areas (interview room and examination/treatment room) next to the clinic or within walking distance. Informing and consenting are conducted in a private room with the door closed to ensure patient's privacy.

The subject will undergo a screening for eligibility (See Sections 3.4.2 and 3.4.3 for Inclusion and Exclusion criteria). The following information will be asked:

- access to telephone and able to provide detailed contact information;
- contraindication to misoprostol;
- history of clotting disorder or use of anticoagulants;
- history of cardiovascular diseases;
- current IUD use;
- current breastfeeding;
- willingness to accept randomization and comply with the study protocol and follow-up visit schedule;
- concurrent participation in other intervention trial(s).

A physical examination, including a pelvic examination, will be conducted by a research clinician. The following information must be recorded:

- vital signs (temperature, pulse, blood pressure, dizziness);
- uterine size, cervical os, active bleeding, product of conception;
- vaginal discharge, cervical motion tenderness, abdominal/adnexal tenderness;

The following lab results must also be obtained:

- hemoglobin test
- Rh status
- transvaginal ultrasound measurement

If a subject is Rh-negative and has not already received Rh-immune globulin, she will be given 50 µg Rh-immune globulin. All subjects will undergo a transvaginal ultrasound to characterize the failed pregnancy unless a complete report from an adequately detailed examination has already been done within 24 hours of enrollment visit. An extra tube of blood (5cc) will be drawn and stored at -70°C for measurement of β-hCG level.

An eligible subject must meet all inclusion criteria and have none of exclusion criteria. A clinical investigator must review all information, check off the Screening Summary form, and ascertain the status of eligibility. If a patient is still eligible after screening, she will be asked to sign a time limited medical record release form to allow us to obtain documentation of any care she may obtain outside the study during the study period. If a potential candidate is a minor (according to local jurisdiction), a parental consent and minor's assent is required prior to enrollment.

The clinical centers will report the numbers of patients approached, screened and reasons for ineligibility to DCC on a monthly basis. The proportion of subjects' race/ethnicity should represent the composition of patient population at each clinical site.

4.1.2 Baseline Interview

After the initial screening, a baseline interview will be conducted. The following information will be collected:

- demographic characteristics;
- reproductive history;
- current pregnancy;
- medical history.

As part of the interview, a person's religion will be asked. This is because personal beliefs may positively or negatively affect one's attitude towards certain treatment and symptoms. This may be one of the factors that determine acceptability of the treatment.

4.1.3 Randomization

After the baseline questionnaire has been administered, the project staff will call the ATRS (described above). The staff will be prompted to answer several key questions. If the patient has met all the requirements, the ATRS will issue a Subject ID

and treatment assignment (D&C or misoprostol) over the phone. A confirmation will be automatically sent to the clinical site by fax. The project staff will record the Subject ID on all forms and the treatment assignment on the Randomization Record. Once a treatment has been assigned to a patient, she is considered to have been enrolled. At anytime after randomization, if the subject decides to withdraw from the study or is lost to follow-up, a Subject Disposition form must be filed.

4.2 PATIENT INITIAL MANAGEMENT

4.2.1 Vacuum Aspiration

Subjects randomized to this treatment will have a suction aspiration performed within 24 hours after randomization. If D&C cannot be done within 24 hours, ultrasound exam should be repeated before the treatment. A standard consent form for D&C will be reviewed and signed by the subject, and she will be given non-steroid anti-inflammatory drugs (NSAID). The procedure will be performed using local anesthesia unless a patient desires intravenous conscious sedation. (If conscious sedation is desired, the patient must have no clinically significant active cardiac or pulmonary disease. A heart and lung examination will be performed to ensure no cardiac arrhythmia is present and the lungs are clear to auscultation. Oxygen saturation and electrocardiograph monitoring will be performed throughout the procedure.)

The suction aspiration will be performed or supervised by an attending physician. After inserting a speculum into the vagina, the cervix and vagina will be cleansed with iodine solution (Hibiclens can be used if the patient is allergic to iodine). An intracervical block will be applied. A tenaculum will be placed on the cervix and the os dilated appropriated, if needed. An appropriate size cannula will be inserted into the uterine cavity and the contents aspirated. A gentle sharp curettage will be performed to confirm the uterus to be empty. The aspirated specimen will be visually inspected for confirmation of the presence of chorionic villi or a gestational sac. If no villi or gestational sac are grossly visible and ectopic pregnancy is suspected, a serum β-hCG level will be measured in 24 hours. If the serum β-hCG level does not decline by at least 50%, the patient will be referred for further evaluation for ectopic pregnancy.

All subjects will be given appropriate post-procedure instructions with instructions to use ibuprofen (or an equivalent NSAID) for cramping as needed. They will be instructed to keep a symptom diary, starting on Day 1 through the end of the study period. They will be asked to bring the diary with them to the clinic every time when they come back for the follow-up visit. They will be informed that the study nurse will call them on Day 8, asking any symptoms, medications and emergency hospital visit after the treatment. A follow-up appointment will be made for Day 15.

4.2.2 Vaginal Misoprostol Administration

After inserting a speculum to expose the cervix, the speculum will be withdrawn

enough to visualize the posterior fornix. Four 200µg of misoprostol tablets (Cytotec; Searle, Skokie, Ill; now by Pharmacia, Piscataway, NJ) will be placed on the posterior blade of the speculum and a cotton swab (Q-tip) will be used to advance the tablets beyond the speculum and into the posterior fornix. The misoprostol will be supplied by the pharmacy at each clinic center. The speculum is then removed and on occasion a cotton swab (Q-tip) is used to replace into the vagina any tablet that might have become lodged on the speculum. The subjects may be discharged home thereafter.

All patients will receive an instruction sheet detailing what to expect after misoprostol administration, and specific information about heavy bleeding (to notify the research office if she soaks 2 maxipads per hour for two consecutive hours) and pain management (use ibuprofen. If stronger analgesic is needed, use codeine), and phone numbers to call if she has any questions or problems. Additionally, the subject will receive 30 tablets of ibuprofen 200 mg and 20 tablets of codeine 30 mg. If the subject is allergic to codeine, Roxicodone (oxycodone 5 mg) 20 tablets will be given instead. Clinical sites will prepare the analgesic kits and give instruction on how to use analgesics. The subjects will be instructed to keep a symptom diary starting on Day 1 through the end of the study period. They will be asked to bring the diary with them to the clinic every time when they come back for a follow-up visit. A follow-up appointment will be made on Day 3.

Pelvic infection, though rare, may cause more serious consequences such as sepsis. To minimize the risk of serious adverse event, all subjects will be instructed to take oral temperature every evening during the study period and record it on the diary. If the body temperature exceeds 100.4°F six hours after misoprostol treatment, the subject should call the doctors or nurses. If pelvic infection is diagnosed, immediate surgical evacuation is indicated. Prompt treatment with i.v. or oral antibiotics is important.

4.3 STUDY FOLLOW-UP VISITS

On Day 3, subjects with misoprostol treatment will return to the clinic for the first follow-up visit. The research staff will review the symptom diary with the patient regarding symptoms, analgesic use and emergency hospital visit after initial dose. A pelvic exam and vaginal sonogram will be performed. A blood sample will be drawn and stored at -70°C for measurement of β-hCG level. If the gestational sac is absent and endometrial lining (anterior-posterior diameter) is less than 30 mm, the expulsion of the product of conception is considered complete. If a gestational sac is still present or the endometrial lining is 30 mm or greater, a second 800 µg of misoprostol will be applied. Patients who receive the second dose of misoprostol will be asked to return to the clinic 5 days later (on Day 8). Those who do not receive the second dose will be informed that the study nurse will call them on Day 8, asking any symptoms and medications following this visit. A follow-up appointment will be made for Day 15.

On Day 8 (for those who receive the second dose of misoprostol), subjects will return to the clinic for the second follow-up visit. The research staff will review the symptom diary with the subject regarding symptoms, analgesic use and emergency hospital visit after the second dose. A pelvic exam will be performed. A blood sample will be drawn and stored at -70°C for measurement of β-hCG level. A vaginal sonogram will measure uterine cavity. If the gestational sac is absent and endometrial lining (anterior-posterior diameter) is less than 30 mm, the expulsion of the product of conception is considered complete. If a gestational sac is still present or the endometrial lining is 30 mm or greater, a D&C will be offered. If the subject declines the D&C treatment, she will be followed clinically. Her treatment will be considered a failure. Otherwise, subjects will be asked to return to the clinic one week later (on Day 15).

Two days before the final visit, research staff will contact the subjects by telephone to remind them of their appointment and ask them to bring in the diary and unused analgesic pills with them.

On Day 15, all subjects will return to the clinic with the diary for the final visit. A detailed questionnaire will be administered regarding symptoms, emergency hospital visit, quality of life, acceptability and cost. The research staff will review the symptom diary with the subject. Unused analgesic pills will be counted. A pelvic examination will be conducted. Hemoglobin level will be measured. Additional 5 cc blood sample will be drawn and stored at -70°C for measurement of β-hCG level. A transvaginal ultrasound will be performed to evaluate the uterine cavity. If sizable product of conception is retained and moderate to heavy vaginal bleeding continues, the subject will be followed clinically by the study physician. The physician may provide additional treatment, if necessary.

On Day 30, all subjects will be contacted by telephone. Information on additional symptoms and treatment during the extended period will be recorded.

Given the potential difficulties in scheduling a follow-up visit on the proposed dates, the following ranges of visit dates are acceptable: Day 2 – Day 5 for Day 3; Day 6 – Day 10 for Day 8; Day 13 – Day 18 for Day 15; and Day 25 – Day 35 for Day 30. Nonetheless, every effort should be made to have follow-up visits on the proposed dates. If a visit can not be made within the acceptable window, it will be recorded as a missing visit. If a patient is unable to come for a follow-up visit within the acceptable window, a telephone interview will be conducted, whenever possible.

4.4 SYMPTOM DIARY

Subjects will be asked to keep a symptom diary through the study period to record episodes of nausea, vomiting, diarrhea, fever, uterine bleeding, pain, analgesic use, emergency hospital visit, and other medication. Pain will be graded on a visual scale of 0 (no pain) to 10 (worst pain in life). Bleeding will be graded as spotting, light,

moderate, heavy and profuse. The subjects will also be asked to record whether they notice any passage of tissue (product of conception) in the blood. They will be instructed to bring the diary with them at each follow-up visit. Subjects will also be given a self-addressed, stamped envelope. If a subject does not return for follow-up visit or forgets to bring the diary with her at the final visit, she will be asked to mail in the diary.

4.5 UNSCHEDULED VISIT

During the study period, subjects may make unscheduled, emergency visit to the research clinic, emergency room or other health care providers for symptoms related to early pregnancy failure or treatment. At each follow-up visit, subjects will be asked if they have made such visits. A form for unscheduled visits will be filed for every such visit. If an unscheduled visit is made outside of the research clinic, every effort will be made to locate medical record for such visits and abstract relevant information. The subject will be asked to keep the scheduled follow-up visit regardless whether she has had any emergency visits.

4.6 CROSSOVER

If a subject decides not to follow the assigned treatment after randomization, this constitutes a crossover. For example, a subject is assigned to D&C but wants misoprostol, and vice versa; or after assignment, she decides not to have any treatment except an expectant management. No matter what method a subject ultimately receives, once she is randomized, she cannot be excluded. In that case, the subjects will be contacted by telephone on Day 8 and Day 30. A telephone interview will be conducted. Medical records will be obtained to collect information on what treatment, if any, is given, whether D&C is used within 30 days, and whether the complete expulsion has been achieved per the protocol definition.

4.7 REPORTING ADVERSE EVENTS

Assessing safety and efficacy of medical management of early pregnancy failure is central to the design and implementation of this trial. Safety is mostly determined from data on frequency of adverse events. Adverse events are defined by the FDA as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events are defined by the FDA as any untoward medical occurrences that: (1) result in death, (2) are life threatening, (3) require (or prolong) hospitalization, (4) cause persistent or significant disability/incapacity, (5) result in congenital anomalies or birth defects, or (6) are other conditions which in the judgement of the investigators represent significant hazards. In compliance with pertinent regulations, information on expected adverse events is summarized in the consent forms.

Data will be collected on all adverse events that are observed or reported during the trial, or within 7 days of cessation of treatment, regardless of the treatment-related assessment and/or clinical observation. In the current study, serious adverse events will include hemorrhage resulting in blood transfusion, uterine perforation requiring surgical procedure, hospitalization, and death. These events will be reported and recorded on Serious Adverse Event Case Report Forms. For all adverse events, the investigator must pursue and obtain adequate information to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event. If an adverse event is persistent at the end of the study, follow-up of the adverse event will continue until the event resolves or stabilizes to a level considered acceptable.

Any serious adverse event must be reported immediately to the NIH Project Officer, the data coordinating center, and the Data and Safety Monitoring Committee regardless of the circumstances or suspected cause if it occurs or comes to the attention of the investigator at any time during the study. Any serious adverse event occurring at any other time after completion of the study must be promptly reported if a causal relationship to study intervention is suspected. The only exception to the above reporting requirements is a serious adverse event occurring during the screening phase prior to randomization.

Each serious adverse event must be evaluated for duration, intensity and relationship to the trial medication/procedure. The action taken and the outcome must also be recorded. The intensity of the serious adverse event will be characterized as mild, moderate or severe. The relationship of the treatment in causing or contributing to the serious adverse event will be characterized as unlikely, possible, probable, or highly probable. Data on serious adverse events will be analyzed and reported to the Data and Safety Monitoring Committee and in the publications concerning the safety of the treatment.

The investigator is obligated to pursue and provide a written report of the event in sufficient detail within three days following the initial report. In addition, the investigator will promptly notify the Institutional Review Board of all serious adverse events within 24 hours, including any significant follow-up information.

4.8 CONFIDENTIALITY

Every effort will be made to protect subjects' confidentiality. Several measures will be taken. First, patient identifiable information, such as patient's name, contact information and hospital record number, will not be recorded on the investigation forms. Only subject ID will be used. No identifiable information will be entered into database or sent to the DCC. Second, all information collected during the study will be kept strictly confidential. All forms and records will be kept in a locked cabinet. Only designated research staff have access to these forms. Finally, information collected in the study

will not be released to any third party without permission of the subjects except as otherwise required by law or regulation.

5. STATISTICAL CONSIDERATIONS

5.1 SAMPLE SIZE AND POWER CALCULATION

The primary outcome of this trial is the efficacy of misoprostol treatment for early pregnancy failure. Unlike the traditional clinical trials which are oriented toward detecting a significant difference between two treatments, this trial is directed toward showing that a more conservative treatment (misoprostol) is equivalent in efficacy to a standard, more costly and invasive treatment (D&C). Therefore, this is an “equivalence trial” or more precisely, "non-inferiority trial". Misoprostol is considered equivalent to D&C if it can be demonstrated that the difference between the uterine evacuation rates is within some range commonly known as the largest acceptable difference. In order to achieve an adequate power, sample size calculation should not based on conventional type I and type II errors but based on the confidence interval concept (Makuch, 1978). The following assumptions are made:

- the success rate for D&C is 98%;
- misoprostol treatment will **not** be more effective than D&C; therefore, one-sided Z-test of proportions will be used;
- the study will have 80% of power;
- the ratio of D&C versus misoprostol is 1 to 2.5 (Note: To compensate for crossover and loss-to-follow, the final ratio will be 1:3. See below for detail.);
- the success rate for misoprostol treatment is 85%, and the lowest acceptable rate is 80%, i.e., if the success rate is lower than 80%, the efficacy of misoprostol treatment will be considered to be inferior to D&C; otherwise, it will be considered to be equivalent to D&C.

Accordingly, the minimal required numbers of subjects for D&C and misoprostol groups are 174 and 435, respectively. Given that subjects assigned to the misoprostol treatment may request D&C for various reasons (assuming up to 10% may cross over) and an additional 15% of subjects may be lost in the follow-up, 569 subjects are needed for the misoprostol group. We choose to recruit 200 patients for the D&C and 600 patients for misoprostol for the convenience of randomization (1:3).

5.2 ANALYSIS PLAN

5.2.1 Interim Data Analysis and Statistical Stopping Guidelines

For both ethical and economic reasons, we plan to conduct one interim analysis after half of the subjects have completed the study. If there is an early indication that misoprostol is equivalent to D&C, the trial may be stopped early. Likewise, if interim analysis suggests that misoprostol is far inferior to D&C, the trial may also be stopped early. The confidence interval approach will be used to sequentially monitor the magnitude and precision of the difference in rate of successful uterine evacuations between using D&C and misoprostol. Specifically, the study should be terminated at

the earliest interim analysis when either 0 or the largest acceptable difference (Δ_{max}) between the two treatments is not contained in the confidence interval (Durrleman, 1990). In this case, since we assume that the lowest acceptable success rate for misoprostol is 80% and that the success rate for D&C is 98%, the largest acceptable difference is 18%. If the interim analysis shows that the 95% confidence interval of the difference in success rate between misoprostol and D&C does not contain both 0 and 18%, the study should be considered for early termination. If the upper limit of the confidence interval is less than 18%, we may stop the study and accept the misoprostol treatment as equivalent to D&C with 95% confidence. Conversely, if the lower limit of the confidence interval is greater than 0%, we may stop the trial and reject the misoprostol treatment and conclude that D&C has a significantly higher efficacy in treating early pregnancy failure than misoprostol with 95% confidence. In calculating the confidence interval, appropriate adjustment will be made using Fleming-Harrington-O'Brian approach (Durrleman, 1990).

The statistical results of the interim analysis will be submitted to the Data and Safety Monitoring Committee. The Committee will make recommendations to NICHD about the actual termination of the trial based on the clinical significance of the statistical findings and other factors such as frequency of adverse events. The Data and Safety Monitoring Committee may also have a separate stopping rule for safety, and such a stopping rule can also be implemented using the above approach.

5.2.2 Final Data Analysis

First, we will examine the demographic and baseline characteristics of the subjects between the D&C and misoprostol groups. If the randomization is executed correctly, we expect no significant difference between theses two groups on these variables. In case there is an imbalance on certain variables (mostly likely by chance) and these variables also affect the outcomes listed below, we will control for these variables using indirect standardization, Mantel-Haenzel stratified analysis or multivariable logistic (for categorical outcome) or linear regression (for continuous outcome). If there is a gross imbalance between the two groups, we will conduct in-depth evaluation to identify factors that may adversely affect randomization. Multivariable logistic and linear regressions will be used to adjust for the imbalance.

Second, we will explore possible difference among clinical sites with regard to the treatment effects. If there is no significant overall difference among the sites (homogeneous), we will pool all sites together, which improves the precision of our findings. However, if there is significant overall difference, we will identify which site (sites) differs from others. Pairwise comparison will be conducted with Scheffe adjustment of significance level. In all following analyses, site will be an independent variable for adjustment.

The following outcomes will be examined using both intent-to-treat and compliant analyses:

- Success rates between misoprostol and D&C for early pregnancy failure;
- Frequency of side effects and serious adverse events between misoprostol and D&C;
- Patient's satisfaction, anxiety, and acceptability of misoprostol comparing to D&C;
- Cost analysis to compare these two treatments;

The patient's satisfaction and anxiety will be assessed using a standard questionnaire on Quality of Life (SF-36). Detailed items, composite score and internal and external validity of SF-36 have been published elsewhere (Ware). We also adopted a series of questions regarding acceptability of the treatments from a previous multicenter randomized clinical trial (Schaff). Answers to these questions will be compared between the two treatment groups using Chi-square tests. We will collect information from the patients on the time spent related to the treatment and monetary expenses incurred to her or her family, which will be considered as indirect cost outside the treatment cost. We will estimate physician and nurse's time and treatment charges from each hospital. The itemized charges will be multiplied by the number of visits and treatments by each subject, which becomes the total direct cost of the treatment. The summary of the direct and indirect costs will be compared between the two treatments.

In addition, we will try to identify factors/predictors for successful misoprostol treatment for early pregnancy failure. In the misoprostol group, we will first examine a number of factors, such as demographic and baseline characteristics, in relation to the success of the treatment. Appropriate transformation, if necessary, will be made. Chi-square test and Student t-test will be used. Variables that are significant in the univariate analysis will be included in a multivariable logistic regression model. Backwards elimination procedure will be used. All analyses will be performed using Statistical Analysis System (SAS).

6. DATA COLLECTION AND MANAGEMENT

6.1 DATA COLLECTION FORMS

The following forms will be used in the Management of Early Pregnancy Failure (MEPF):

Form A	Hospital Application
Form B	ATRS Worksheet
Form D	Inclusion Criteria Checklist
Form E	Exclusion Criteria Checklist
Form 00	Patient Contact Information
Form 01	Screening
Form 02	Enrollment Interview
Form 03	Physical Examination, Laboratory Work, Vaginal Ultrasound
Form 05	Treatment – Misoprostol
Form 06	Treatment – D&C
Form 07	Symptom Interview
Form 08	Scheduled Study Visit
Form 09	Serious Adverse Event
Form 10	Unscheduled Visit
Form 12P	Symptom Diary
Form 12	Symptom Diary Coding Form
Form 13	Quality of Life, Acceptability and Cost
Form 14	Missed Contact
Form 16	Screening Log

6.2 CENTRALIZED DATA MANAGEMENT SYSTEM

The DCC will create and maintain the data entry form and store the database in a server. Authorized research staff at the clinical centers can have access to the data entry form through the web site. After a form is completed, the research staff will enter the data through their computer terminals at the clinical site. Data should be entered within 30 days after collection. When a subject completes her visits and all data are computerized, the clinical center will send the completed file to DCC. DCC staff will monitor the process and edit data centrally. Key information will be entered once again at DCC.

Large documents and reports will be posted on the study web site. This will include the Protocol, Manual of Operations, forms and selected reports and minutes. Study activities, such as meeting schedule and site visit, will also be posted on the web site. Research staff at the clinical centers will be given passwords to get access to the web contents.

Due to the importance of data security, access to all computer files and programs will be restricted to authorized personnel through the use of passwords and automatic access control at the file level. DCC will use a secure socket for this study (an encoding device that is used to send confidential information, e.g., credit card numbers). This will insure that all data being sent over the Internet are properly encrypted using standardized encryption protocols. Appropriate firewall and virus scanning software are installed and updated at least monthly. Subject identification (e.g., name and address) will not be entered into computer and the paper document will only be kept in the clinical centers.

6.3 QUALITY CONTROL PROCEDURES

To assure a timely and accurate data collection through the study, several steps will be taken. First, the Principal Investigators (PI) and Study Managers from the clinical centers will be required to attend a central training session before study recruitment begins. The PIs are responsible for training co-investigators, nurses and sonographers, and making final assessment on success or failure of the treatment and decisions regarding further treatment. The PIs have the overall responsibility of following study protocol and assuring the quality of the data. The Study Managers will train other research staff on the data collection procedures, randomization and data entry. The PIs and the Study Managers will review all the data collection forms in the pilot study and identify potential problems.

Second, the DCC will establish and update a communication system among all parties involved, which includes a Web Site, e-mail list, telephone and fax numbers. PIs and research staff will be informed of any decisions, changes of the forms and procedures promptly. Monthly recruitment reports will be prepared by the DCC and sent to NICHD Project Officer, PIs and Study Managers at the clinical centers. It will report the number of women screened and enrolled by month and by clinical center. Prompt inquiries on incomplete, missing or illogical data entry will be generated by the DCC and sent to the clinical site for clarification. The inquiries and potential problems must be handled by research staff at the clinical sites in a timely manner. The computer system will automatically record any changes in the data base made by the clinical center staff or by the data center staff. Monthly data log will be generated to monitor data entry quality. The DCC will prepare a Performance Report detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol by clinical centers. Prior to the Data and Safety Monitoring Committee meeting, the DCC will produce a detailed report, which includes clinical center performance information with respect to data quality, timeliness of data submission and protocol adherence.

Finally, during the study period, investigators will have regular telephone conferences (once a month for the first three months and once every two months thereafter) and meetings (once every six months). The Project Officer and DCC staff will conduct site visits once every six months.

7. STUDY ADMINISTRATION

7.1 ORGANIZATION AND FUNDING

7.1.1 National Institute of Child Health and Human Development

This study is being conducted by the Epidemiology Branch, National Institute of Child Health and Human Development, National Institutes of Health, in collaboration with four clinical centers and a data coordinating center. The Project Officer, serving as the Principal Investigator for the overall study, is responsible for the study design, implementation, data quality and information dissemination. The study is funded by the National Institute of Child Health and Human Development through contracts (N01-HD-1-332[1-5]).

7.1.2 Participating Clinical Centers

The Principal Investigators of the clinical centers have agreed to abide by the study protocol, to have comparable staff, facilities and equipment and to ensure the proper conduct of the study at each of their center(s) including: recruitment and treatment of the patients as specified in the protocol, accurate data collection and the transmission of information to the DCC.

7.1.3 Data Coordinating Center

The DCC is responsible for logistics of study coordination, data management, study monitoring, quality control measures and descriptive data analysis.

7.2 COMMITTEES

7.2.1 Steering Committee

This committee consists of six members: the NICHD Project Officer, the Principal Investigator from each of the four clinical centers and the Data Coordinating Center. The Steering Committee has the responsibility for developing the study protocol and monitoring study implementation, recruitment and protocol adherence. The Committee receives recommendations from the Data and Safety Monitoring Committee.

7.2.2 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee is composed of five members: four physicians in related research area and one biostatistician. This committee will be charged with reviewing the protocol with respect to ethical and safety standards and making recommendations if necessary. During the study, the Committee will meet periodically to review safety issues and to monitor clinical center performance in execution of the protocol. Prior to each meeting, a formal, detailed report will be

generated by the DCC with emphasis placed on safety issues and center performance. At the beginning of each meeting, the NICHD Project Officer and the DCC Principal Investigator will present the study progress and answer any questions.

8. STUDY TIMETABLE

November 2001 -- February 2002	Obtain FDA, OMB, IRB and DSMC Approvals
March 2002	Start to Recruit Subjects
March 2003	Interim Analysis
December 2003	Complete the Data Collection
January – June 2004	Data Cleaning and Analysis

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